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FREQUENCY ESTIMATION OF ELECTRO-ISLET-GRAPHY

Field of the Invention

The present invention relates generally to methods and systems for processing electro-physiological signals and, more particularly, concerns the detection and analysis of 15 electrical activity related to blood glucose concentration.

Background of the Invention

Blood glucose level monitoring is of great importance for diabetics. Continuous monitoring of the glucose level can greatly reduce the medical complications, that 20 are caused by metabolic imbalance.

The Islets of Langerhans are located in the pancreas, and are responsible for the manufacture of insulin in the human body. An islet is a cluster of many cells. The Beta cells within the islets respond to glucose in bursts of electrical activity. The use of such islets, derived from the pancreas of donor animals, in a blood glucose monitor is disclosed in U.S. 25 Patent 5,101,814. Electro-Islet-Graphy (EIG) is the measurement of the electrical activity of the islets of Langerhans. The present invention utilizes EIG to provide a continuous blood glucose level sensor.

Studies demonstrate a clear correlation between the fundamental frequency of the EIG signal, and the glucose level in the medium surrounding the islet. Hence, the 30 estimation of the fundamental frequency of Electro-Islet-Graphy   is of significant practical value.

The fundamental frequency is defined as the frequency of the "events" of the EIG. An "event" is believed to represent the synchronized electrical activity of the cells in the islet. By analogy to an ECG. an "event" in EIG is comparable to a the heart cycle (the PQRST

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comlex).

Although it is believed that EIG processing has not been performed by any entity but the owner the present patent application, one might attempt to detect the events directly, and then to calculate the fundamental frequency. The problem with this approach is
5 that the shape and size of EIG "events" varies greatly, and therefore reliable and robust event detection is difficult to achieve.

In accordance with the present invention, the fundamental frequency of EIG events is determined directly, without first detecting the individual events themselves. All these algorithms must use an analysis window containing more than one event. The present
10 invention utilizes techniques similar to those utilized to detect and estimate pitch in speech processing

The invention is based on two important biological discoveries. The first is that the EIG is generated by a functional pace maker. The second is that the EIG signal is *quasi-periodic* most of the time. Pitch detection algorithms are used, because of the
15 essentially quasi-periodic nature of the EIG signal. By *quasi-periodic* we mean that (1) the intervals between successive events are not exactly identical, but may vary slightly and (2) the amplitude and shape of successive events may also exhibit some variance.

Several pitch detection algorithms were tested. Three of them achieved good results: Autocorrelation, Segmented Autocorrelation and Harmonic Peaks analysis. The
20 preferred embodiments of the invention focus on algorithms that are based on the Autocorrelation methods.

The preferred version of the algorithm comprises the following steps:

• Detection of the non-EIG signals. The signal may include non-EIG segments, such
25 as artifacts and silences. The signal is scanned and the non-EIG segments are marked and ignored.

  • The signal is divided into overlapping analysis windows, each four seconds long and each has a 75% overlap with the adjacent windows. The analysis window contains more than one event.

30   • A modified form of an Autocorrelation transform of the type used for pitch detection in speech processing is applied to a single analysis window. This step is repeated for each analysis window.

- The fundamental frequency is derived from the autocorrelation values of the analysis window. Usually the fundamental frequency is indicated by the largest autocorrelation value. This step is repeated for each analysis window.

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- A postprocessor is used to "smooth out" the results of all the individual analysis windows. The previously marked non-EIG segments (artifacts and silences) are added in this phase.

To produce the modified autocorrelation transform, the existing autocorrelation based algorithm was adapted to EIG in the following ways:

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- An improved algorithm was devised for determining pitch from the autocorrelation values. The algorithm usually chooses the highest autocorrelation peak (value). In EIG we found that sometimes the true pitch is not represented by a peak, but rather by a valley between several adjacent peaks. An algorithm was devised to locate those

15 cases, and to correctly estimate the pitch. We refer to this phenomena as a "volcano" shaped autocorrelation graph, because the center of the "mountain" is found on lower ground.

- A voiced/unvoiced decision mechanism was adapted from speech processing. The "unvoiced" EIG segments were defined as a non-signals (undecided segments). A postprocessor was used to decide on

20 the pitch of those undecided segments. Although unvoiced speech segments do exist, "unvoiced" EIG segments are a virtual non-signal, and do not really exist.

- A special pre-processing algorithm was devised. The signal undergoes

25 convolution so as to increase the width of the event. This is unlike speech pre-processing, which is aimed at enhancing the high amplitude portions and/or filtering out the formants. This preprocessing technique is referred to as "fattening".

- A very long analysis window of 4 seconds was used, in order to find

30 frequencies ranging from 0.25 Hz to 5 Hz. In speech it is customary to use a window of about 30 milliseconds, in order to find frequencies ranging from 80 Hz to 300 Hz.

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The invention also contemplates the use of a Segmented Autocorrelation algorithm. This is considered to be the best method for EIG, but other methods are also adequate. Segmented autocorrelation is described in "Pitch detection of speech signals using Segmented Autocorrelation"/ I. A. Atkinson, A. M. Kondoz, B.G. Evans/ Electronics Letters

5   Vol. 31 No. 7 pp. 533-535/March 1995.

Brief Description of the Drawings

The foregoing brief description, as well as further objects, features, and advantages of the present invention will be understood more completely from the following

10   detailed description of a presently preferred embodiment, with reference being had to the accompanying drawings, in which:

FIG. 1 is a functional block diagram showing an overview of the process of the preferred embodiment;

FIG. 2 is a flowchart describing the pre-detectors, the silence detector and the

15   artifact detector;

FIG. 3 is a flowchart describing fundamental frequency estimation of an individual analysis window;

FIG. 4 is a flowchart expansion of one of the block 25 of FIG 3 and describes the decision algorithm of the fundamental frequency estimator; and

20   FIG. 5 is a flowchart describing the post-processing phase algorithms, which combine information from neighboring analysis windows in order to correct local estimation errors.

Detailed Description of the Preferred Embodiment

25   The preferred embodiment of the invention will now be described in detail with reference to the accompanying drawings. First a schematic overview of the preferred embodiment of a process and system for fundamental frequency estimation of EIG is presented in **FIG. 1**. The algorithm comprises of the following steps:

30   a.   Detection of the non-EIG signals. The signal may include non-EIG segments, such as artifacts and silences. The signal is scanned and the non-EIG segments are marked and ignored. A silence detector 1 and an artifact detector 2 are used. An "artifact" is a

dominant interference noise signal, which severely corrupts the EIG signal.

b.   The signal is divided into overlapping analysis windows. Each window is 4 seconds

5   long and has a 75% overlap with the adjacent windows. The analysis window must

contain more than one event. It is contemplated that the analysis window could be as

much as forty times the interval between successive events.

c.   The autocorrelation transform **4** is applied to a single analysis window. This step is

repeated for each analysis window. pre-processing **3** is optional, and is not used in the

10   preferred embodiment.

d.   The fundamental frequency is derived from the autocorrelation values of the analysis

window **5**. Usually the fundamental frequency is indicated by the largest

autocorrelation value. A sureness measure **6** is computed for the estimated

15   fundamental frequency of the analysis window. This step is repeated for each analysis

window.

e.   A postprocessor **7** is used to "smooth out" the results of all the individual analysis

windows. The previously marked non-EIG segments (artifacts and silences) are

20   added in this phase.

f.   The output is the estimated fundamental frequency of the signal **8**.

The preferred embodiment of the invention includes software which preferably

25   runs on a Pentium PC, using the Windows 95 operating system.   The algorithm was

implemented on the "Matlab" software by "The Mathworks Inc." The algorithm was written

in the Matlab language, and runs within the Matlab program shell. It also requires the "Digital

Signal Processing Toolbox" for Matlab, by "The Mathworks Inc."

FIG 2. is a flowchart describing the pre-detectors. The silence detector (**11**

30   , **12** , **13**) involves two steps. In the first step **11** an amplitude related measure is computed for

each second, and in the second step **12** the amplitude related measure is compared to a fixed

threshold. "Sig" is the raw digital input signal. It is the raw signal recorded from the islet,

after an Analog to Digital conversion. In block 11 each one second window is examined. "Max(Sig)" is the maximum sample value within the examined one second window. "Min(Sig)" is the minimum of the samples' values within the examined one second window. As "Sig" is always a real number, the real maximum and minimum are computed. If the

5   measure is below the threshold for more than 5 seconds, then the segment is classified as silence 13. The threshold depends on the measurement equipment and environment. It also depends on the digitizing scale. In the preferred embodiment the maximum amplitude of the EIG signal is approximately 4000 amplitude units, so a threshold of 100 amplitude units is used. An "amplitude unit" is the amplitude difference between two adjacent quantization

10   levels of the Analog to Digital converter. In the preferred embodiment one "amplitude unit" corresponds to 0.25 Micro-Volt of the original electrical signal. "Original" means before amplification.

       The artifact detector (14, 15, 16, 17) involves two steps. In the first step 14 the signal is compared to an adaptive threshold. The adaptive threshold is computed using a

15   300 second long recording, by the following computation:

       A high reference is defined as the 99.833 percentile of the
       histogram of the amplitude values of the 300 second long
       recording.

20   A low reference is defined as the 0.167 percentile of the
       histogram of the amplitude values of the 300 second long
       recording.

       An amplitude reference is defined as the high reference minus
25   the low reference.

       A high threshold is defined as the high reference plus the
       amplitude reference.

30   A low threshold is defined as the low reference minus the
       amplitude reference.

The "histogram" used in block **14** is generated by simply sorting all the sample values ("amplitudes") of a 300 second long recording. The sorting is done from the smallest value to the largest value. Based on those sorted values the two references are derived. The "high reference" is the 99.833 percentile of the sorted values. The "low reference" is the 0.167

5 percentile of the sorted values. The term "histogram" refers to the sorting of the values, and can be replaced by the term "sorted amplitude values."

The second step **15** involves checking whether there are samples in which the signal's amplitude is above the high threshold or below the low threshold. If such samples are found then they are classified as containing an artifact **16**. The remaining samples **17** are not

10 classified as an artifact or as a silence.

FIG. 3 contains a flowchart describing the steps that are performed on each analysis window. Each analysis window is 4 seconds long. Overlapping analysis windows are used. There is a 3 second overlap between two successive windows. Analysis windows containing either silences or artifacts are not analyzed. The analysis windows are described

15 in block 21, and are represented mathematically by the following notation:

$x(n)$ are the raw digital samples of the signal. We earlier referred to this raw input signal as "Sig." This is the same signal, only that here a more strict mathematical notation is used. The analysis window contains 4 seconds of signal. The

20 sampling frequency ("FS") in the preferred embodiment is 100 Hz, therefore the analysis window contains 400 samples. This is marked by "N(Window length)=400." The first sample in the analysis window is $x(l)$, where "l" is the index of the sample. Therefore the last sample in the analysis window is

25 $x(l+399)=x(l+N-1)$. Therefore the analysis window is described by the samples it contains from $x(l)$ to $x(l+N-1)$.

Preprocessing **22** may be used, but it is not implemented in the preferred embodiment.

A rectangular window **23** is applied to the samples, and a normalized biased

30 autocorrelation transform **24** is computed. It is represented mathematically by the following equation:

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$$\varphi(m) = \frac{1}{\sum_{k=0}^{N-1} [x(k+1)w(k)]^2} \sum_{n=0}^{N-|m|-1} [x(n+1)w(n)][x(n+l+m)w(n+m)] \qquad \text{(1)}$$

where "w(n)" is the windowing function." As "w(n)" is a rectangular window, as described

5   in block 23, it is equivalent to "1" within the analysis window:

w(n)= 1   0≤n≤N-1

0   *Otherwise*

The autocorrelation transform is further described in the book "Digital Processing of Speech

Signals", L.R. Rabiner and R.W. Schafer, 1978, pp. 141-164. The fundamental frequency

10   decision algorithm 25 is described in more detail in **FIG. 4**.

We will now refer to **FIG. 4** and later return to **FIG. 3**.

FIG. 4 is a flowchart describing the fundamental frequency decision algorithm.

Actually it decides on the fundamental period, from which the fundamental frequency can be

derived. An improved algorithm was devised for determining the fundamental frequency from

15   the autocorrelation values. In typical algorithms the highest autocorrelation peak (value) is

usually chosen. In EIG, it was found that sometimes the true pitch is not represented by a

peak, but rather by a valley between several adjacent peaks. An algorithm was devised to

locate those cases, and to estimate the pitch correctly. We refer to this phenomenon as a

"volcano" shaped autocorrelation graph, because the center of the "mountain" is found on

20   lower ground.

The input to the decision algorithm is a vector containing the autocorrelation

coefficients 31. Steps 32 and 33 find the 5 highest extreme points within the allowed

frequency range. A "volcano" effect detector 34 checks first whether one of the highest peaks

is found in a suspected "volcano" area. If such a peak is found, it's index (*i*) is passed on in

25   order to check the peak's amplitude 35 compared to the amplitude of the highest peak. If the

result is positive then a "volcano" is detected 36 and the estimated fundamental period is half

of the autocorrelation lag corresponding to the highest peak. The autocorrelation is

represented by equation (1) above. *m* is the "autocorrelation lag." It is the lag between the

two segments on which the correlation is computed. The first segment is $x(n+l)$ to $x(n+l+N-$

30    $|m|-1)$ and the second segment is $x(n+l+m)$ to $(x+l+m+N-|m|-1)$. Also, see "Digital

Processing of Speech Signals", L.R. Rabiner and R.W. Schafer, 1978, pp. 141-164.

A pitch halving detection algorithm 37 first checks the ratio of the

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autocorrelation coefficients' lag 37, and then their amplitudes 38. If one of the highest peaks fulfills both those conditions then it is chosen as the estimated fundamental period 39. If both the "volcano" detector and the pitch halving detector produced negative results, then the estimated fundamental period is assumed to be the lag of the highest autocorrelation peak 40.

5   The output of the fundamental period decision algorithm of **FIG. 4** is the estimated fundamental period. This output is returned to block 26 in **FIG. 3**.

A "voiced" decision mechanism 26 (Fig. 3) is used to decide whether the fundamental frequency should be estimated in the current analysis window. If the maximum autocorrelation coefficient in the allowed lag range (a lag of 20 to 333 samples) is below 0.3,

10   then the analysis window is classified as "unvoiced", and no fundamental frequency is estimated 27. In that case a sureness grade of zero is given to the analysis window.

The voiced / unvoiced decision mechanism was adapted from speech processing. The "unvoiced" EIG segments were defined as non-signals (undecided segments). The postprocessor will be used in later stages to decide on the fundamental frequency of

15   those undecided segments. Note that unvoiced speech segments do exist, while "unvoiced" EIG segments are a virtual non-signal, and do not really exist.

If the current analysis window is not classified as "unvoiced" then the estimation process continues, and a sureness grade is calculated for the current analysis window 28. A higher sureness grade indicates that there is a higher probability that the

20   fundamental frequency was estimated correctly. For each analysis window several outputs 29 are returned:

1.   The estimated fundamental period- this value is not returned if the analysis window is classified as "unvoiced";

2.   A "voiced"/"unvoiced" decision- specifies whether the fundamental period

25   was estimated in the analysis window; and

3.   A sureness grade- this value is not returned if the analysis window is classified as "unvoiced".

FIG. 5 describes the final stage of the estimation process: the postprocessor. The postprocessor combines all the acquired data 41 into a fundamental frequency estimate

30   of the raw signal. The postprocessor operates on a 300 second long recording of the raw signal. The first step 42 is to convert all the estimated fundamental period values into estimated fundamental frequency ("Pitch") values. The output of this stage is a fundamental

frequency estimate, in Hertz, for every "voiced" analysis window. The next step **43** inserts

the previously detected silence segments **1** into the fundamental frequency estimation results.

The fundamental frequency is assigned a value of 0 (Hz) in all windows containing only

silences. All analysis windows containing an unlikely fundamental frequency estimate are

5   marked as "unvoiced" in the next step **44**.

The next step **45** assigns a fundamental frequency ("pitch") value to the

"unvoiced" segments. The postprocessor loops once over all the analysis windows. It assigns

Pitch values to all "unvoiced" windows (windows containing artifacts are also treated as

"unvoiced"). Pitch values are derived from an average of the pitch values of the neighboring

10   windows. Some minor data dependent modifications can be added in order to create a smarter

averaging method, but those are minor changes which are very data dependent. A pitch

halving / doubling error correcting mechanism is then applied **46**. The algorithm loops once

over all the analysis windows. If the Pitch of the current window is half or double the average

of the neighboring windows, then the current Pitch is taken as a smart average of the

15   neighbors. The term "smart averaging" refers to the average of an ensemble of numbers, after

the extreme values are removed. For example: We can define a "smart average" of 8 numbers

in the following way:

1.   Remove the maximal and minimal numbers and

2.   Compute the average of the remaining 6 numbers.

20   This "smart averaging" method is used in order to achieve more stable and robust results.

The final step **47** looks for an analysis window having a pitch which is

significantly different than its neighbors. The algorithm loops once over all the analysis

windows. If the Pitch of the current window, is 35% greater or smaller than the average of the

neighboring windows, then the current Pitch is taken as a smart average of the neighbors.

25   The final output **48** of the entire fundamental frequency estimation process is

a fundamental frequency value for each analysis window.

Although a preferred embodiment of the invention has been disclosed for

illustrative purposes, those skilled in the art will appreciate that many additions, modifications

and substitutions are possible without departing from the scope and spirit of the invention.

30   For example, the principles and applications of the invention are not limited to the particular

biological phenomenon described. They could be utilized equally well, for example, for

measuring an optical signal from living cells of a muscle or the electrical signals of neurons,

or various signals produced by similar or other biological micro-structures. In particular, it is contemplated that the invention could find utility in any application where a cell or other biological micro-structure is moved outside its natural environment and used as a biological sensor.